Computational Toxicology Framework: Enhancing Quantitative Risk Assessment

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What is Quantitative Risk Assessment?

- As used in the Framework, Quantitative Risk Assessment (QRA) refers to an assessment that provides a numerical representation of risk

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Current EPA Approaches to Human Health QRA

- Standard EPA approach
  - For non-cancer effects, assumption of a threshold dose below which response does not occur
  - For cancer endpoints, assumption of no threshold and linear extrapolation to responses at low doses
- New directions
  - Development of consistent approaches for cancer and non-cancer endpoints based on plausible biological mechanisms (e.g., see EPA's Draft Guidelines for Carcinogen Risk Assessment)

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Current EPA Approaches to Ecological QRA

- Standard testing protocols for acute and chronic effects using test species
- Peak estimated environmental concentrations compared to EC_{50}s and LC_{50}s for selected exposure periods
- Ecological QRA
  - Assesses risks to many species
  - Focuses on populations rather than individuals

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How can computational approaches reduce uncertainty in EPA's risk assessments?

- Quantitative Structure Activity Relationships (QSAR) to estimate concern levels
- Systems biology modeling approaches
- Genomics, proteomics, metabonomics technologies

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QSARs

- Examples of current EPA research on use of QSARs for estimating quantitative toxicity values for chemicals with no experimental data
  - 96-hr LC_{50} values for fathead minnows
  - Oral rat LD_{50} values
  - Toxicity benchmarks for use in human health risk assessment
  - Fate/transport and PBPK parameters for models used in risk assessment
- The framework envisions that computational toxicology methods will be used to develop more accurate QSAR methods based on classification by toxicity pathway

Systems Biology: Examples of Current EPA Research

- EPA Request for Applications for Research on Systems Biology (closing January 21, 2004)
  - Develop models of normal and perturbed systems in rat or small fish toxicology model of hypothalamic-pituitary-gonadal or hypothalamic-pituitary-thyroid axes
  - Cross-species extrapolation of the perturbed axes
    - From rats to humans, or
    - From a small fish toxicology model to other vertebrates using systems biology models of normal and perturbed systems

Systems Biology: Examples of Current EPA Research (cont'd)

- Development of components of systems biology approaches
  - Physiologically-based pharmacokinetic modeling
  - Biologically-based dose response modeling

Systems Biology: Examples of Risk Assessment Applications

- Systems Biology Models
  - Develop models of normal systems (cell, organ system, or organism) from models of component parts
  - Simulate perturbations in the system as a result of exposure to environmental agents at various dose levels to predict quantitative dose-response relationship
- Extrapolation between species
  - Predict metabolic pathways and internal doses of metabolites in each species using PBPK/BBDR models
  - Compare dosimetry information to decide whether extrapolation is appropriate

Genomics, Proteomics, Metabonomics: Current EPA Research

Improve interspecies extrapolation

- Use gene sequencing to isolate genes, produce proteins and compare protein (androgen receptor) function among different classes of vertebrates

Design and Ongoing Studies

Plan

- Obtain Animal Tissues
- Prepare cDNA Library
- Isolate ER or AR
- Sequence ER or AR
- Express ER or AR
- ER or AR Function
- Compare Structure/Function Across Species

Status


Japanese Quail


Daphnia Magna


American Alligator


Northern Leopard Frog


Mud Snail


Fathead Minnow ER

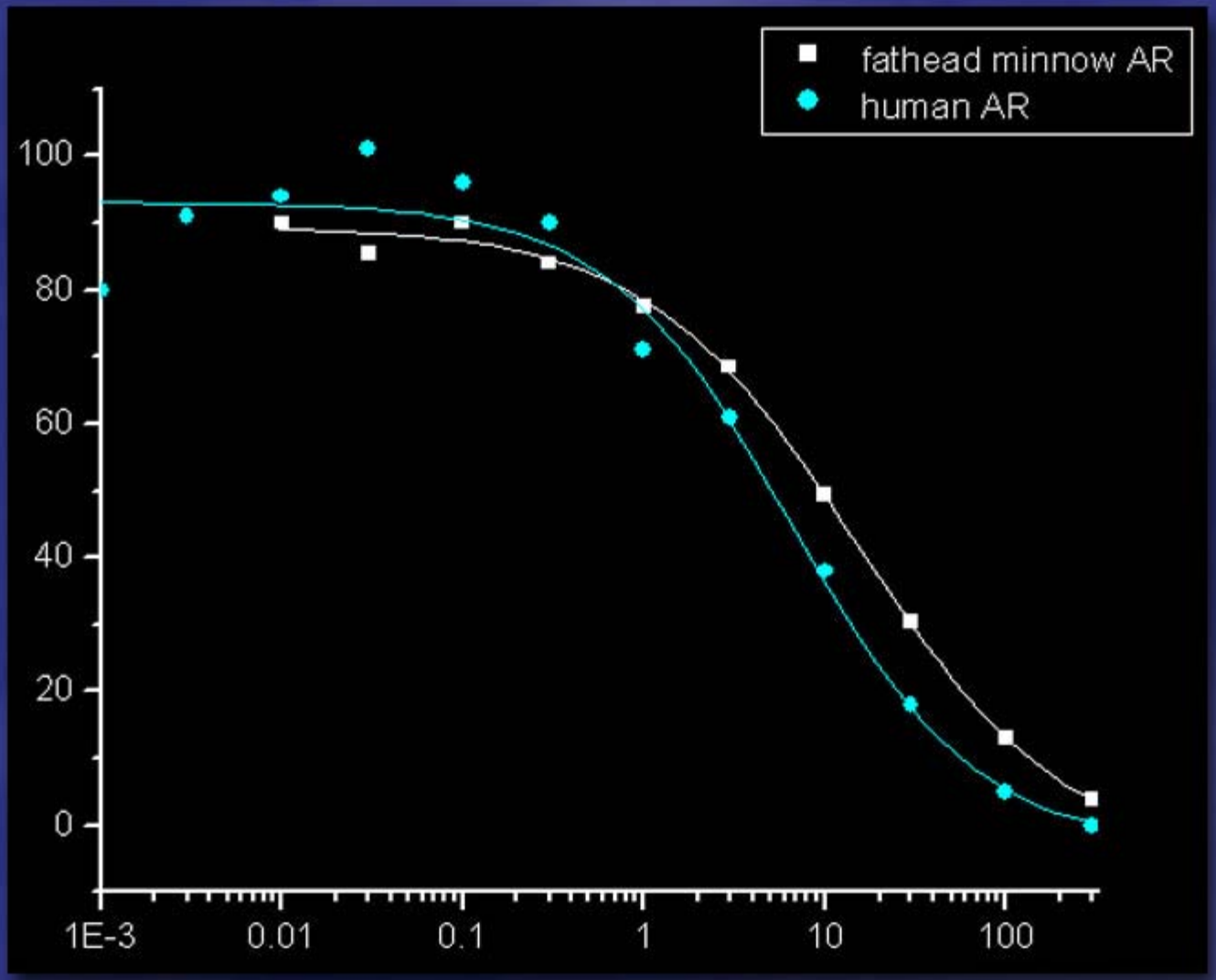

Rainbow Trout ER


Rainbow Trout AR


Fathead Minnow AR

?

17β-Trenbolone binds to both the human and fathead minnow androgen receptors with similar affinity



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Genomics, Proteomics, Metabonomics: Current EPA Research

- Study of phthalate ester-induced malformations associated with changes in gene expression and steroid hormone malformation in fetal rat testis during sexual differentiation
  - Potential to use fetal endocrine and gene expression data to set low dose NOAELs for phthalates if these data can be shown to be predictors of malformations in fetal tissues
- Research to assess the potential developmental effects of Drinking Water contaminants. Examination of changes in phosphorylation of proteins and changes in protein expression using a 2-D gel approach in embryos.

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Other Potential Applications to QRA

- Define shape of the dose response at low doses using molecular indicators of response
- Assess toxicity of mixtures
- Integrated cross-species assessments

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